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No. 06-

IN THE

Supreme Court of the United States

DR. REDDY'S LABORATORIES, LTD.,

Petitioner,

v.

ELI LILLY AND COMPANY and
LILLY INDUSTRIES LIMITED,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Prior to this Court's April 30, 2007 decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. __, 127 S. Ct. 1727 (2007), the United States Court of Appeals for the Federal Circuit applied a particularly restrictive version of its "teaching-suggestion-motivation" test for obviousness in this case and found patent claims to the chemical compound olanzapine not obvious over closely related prior art chemical compounds. The Court's *KSR* decision casts substantial doubt on the rigid manner in which the Federal Circuit applied its teaching-suggestion-motivation test, whereby the Federal Circuit ignored the uncontested actual facts regarding the development of olanzapine in favor of suggestions in some literature that purportedly taught away from an entire class of prior art compounds.

The question presented is:

Whether the Federal Circuit's application of its teaching-suggestion-motivation test in a manner that unduly constricted its obviousness analysis merits summarily granting the petition, vacating the judgment, and remanding for further consideration in view of *KSR*?

PARTIES TO THE PROCEEDINGS

The Petitioner before this Court in the instant writ of certiorari is Dr. Reddy's Laboratories, Ltd. In addition, Teva Pharmaceuticals USA, Inc. and Zenith Goldline Pharmaceuticals, Inc. (now known as Ivax Pharmaceuticals, Inc.), the other two defendants-appellants in the United States Court of Appeals for the Federal Circuit and in the United States District Court for the Southern District of Indiana, separately filed a Petition for a Writ of Certiorari, which was docketed on June 11, 2007 as No. 06-1642. The Respondents are Eli Lilly and Company and Lilly Industries Limited.

CORPORATE DISCLOSURE STATEMENT

Petitioner, Dr. Reddy's Laboratories, Ltd., has no parent corporation and no publicly held company owns 10% or more of its stock.

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PETITION FOR A WRIT OF CERTIORARI

Dr. Reddy's Laboratories, Ltd. ("DRL") respectfully petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit.

OPINIONS BELOW

The opinion of the United States District Court for the Southern District of Indiana was issued on April 14, 2005, and is reported at 364 F. Supp. 2d 820 (App. 27a-271a).

The panel opinion of the United States Court of Appeals for the Federal Circuit was issued on December 26, 2006, and is reported at 471 F.3d 1369 (App. 1a-26a). The Federal Circuit's order denying panel rehearing and rehearing *en banc* issued on March 29, 2007, and is not reported (App. 272a-273a).

JURISDICTION

The opinion of the United States Court of Appeals for the Federal Circuit was issued on December 26, 2006 (App. 1a-26a). The Federal Circuit's order denying Appellants' petition for panel rehearing and rehearing *en banc* was issued on March 29, 2007 (App. 272a-273a). The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

CONSTITUTIONAL AND STATUTORY PROVISIONS INVOLVED

Section 103(a) of Title 35, United States Code, provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

STATEMENT OF THE CASE

1. The patent at issue in this case is United States Patent No. 5,229,382 ("the '382 patent"). The '382 patent claims both the chemical compound olanzapine and the use of olanzapine to treat schizophrenia. DRL filed Abbreviated New Drug Applications ("ANDAs") with the United States Food and Drug Administration ("FDA") seeking approval to market a generic version of olanzapine prior to expiration of the '382 patent. Lilly brought suit against DRL for infringement under 35 U.S.C. § 271(e)(2) in the United States District Court for the Southern District of Indiana.

2. Olanzapine is an atypical antipsychotic that has been approved by the FDA for the treatment of schizophrenia, and is marketed under the name Zyprexa®. App. 30a. Olanzapine was the second safe atypical antipsychotic drug to receive FDA approval. *See* App. 86a. The first atypical antipsychotic drug, clozapine, had significant safety issues. App. 33a.

Olanzapine belongs to a family of compounds known as the thienobenzodiazepines, and was first synthesized by Lilly research chemists in 1982. App. 40a.

When olanzapine was synthesized, Lilly was not working from a blank slate. Lilly had spent several years and invested considerable effort in research directed at developing an antipsychotic drug in the thienobenzodiazepine family. Prior to making olanzapine, Lilly had advanced into development two compounds that were structurally-related to olanzapine – ethyl flumezapine and flumezapine. In 1978, Lilly had also obtained two patents that covered numerous thienobenzodiazepines asserted to be useful in the treatment of schizophrenia – United States Patent No. 4,115,568 and United States Patent No. 4,115,574 ("the '574 patent"). App. 35a-39a. In addition, Lilly had published the results of some of its work with the thienobenzodiazepines in a series of articles ("the Chakrabarti publications") reporting on the structure-activity relationship of these compounds. App. 68a-70a.

The two compounds Lilly had advanced into development before olanzapine – ethyl flumezapine and flumezapine – were disclosed and claimed in the '574 patent. Ethyl olanzapine (also known as Compound '222) was also disclosed in the '574 patent. App. 66a-67a. This compound was the first in a long list of compounds that exemplified the compounds of the invention. C.A. A19653.[1] The synthesis of Compound '222 was also included as one of the examples of the patent. C.A. A19667. Thus, as shown in the figure, by the time Lilly decided to synthesize olanzapine, the '574 patent had placed in the hands of a person of ordinary skill in the art the closest structurally-related compounds to olanzapine – flumezapine and ethyl olanzapine:

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1. C.A. A___ refers to the record before the United States Court of Appeals for the Federal Circuit.

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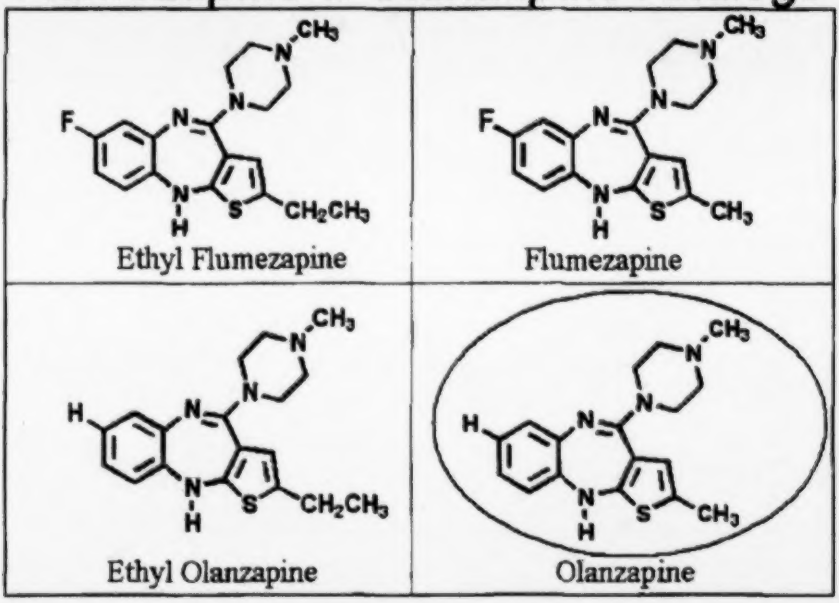
Flumezapine & Olanzapine Analogs



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Indeed, the parallels between olanzapine and the prior art compounds cannot be denied. Flumezapine and olanzapine each has a methyl ($-CH_3$) substituent on the lower right-hand side of the thienobenzodiazepine molecule (known to organic chemists as the 2-position), while ethyl flumezapine and ethyl olanzapine each has an ethyl ($-CH_2CH_3$) substituent – instead of a methyl – at that same position. In addition, ethyl flumezapine and flumezapine each has a fluorine atom (F) on the left-hand side of the thienobenzodiazepine molecule (known to organic chemists as the 7-position), while ethyl olanzapine and olanzapine each has a hydrogen atom (H) at that same position.

In addition to the teachings in the '574 patent, the Chakrabarti publications also contained disclosures about the effect of certain substituents on the thienobenzodiazapines.

The publications taught the effect of a short-alkyl substitution on the antipsychotic activity of these compounds. The Chakrabarti 1980 publication taught that a short-alkyl substitution at the 2-position enhanced antipsychotic activity. A short-alkyl substitution was defined as a methyl, ethyl, or iso-propyl substituent. Later publications in 1982 and 1989 were more emphatic about the result of such a change in the compounds. App. 68a-70a. Indeed, by the time of the 1989 publication, Lilly researchers stated without equivocation that a short-alkyl substitution "greatly enhanced activity" of these compounds. C.A. A19689.

The same chemists at Lilly who had worked on flumezapine and ethyl flumezapine were also responsible for synthesizing olanzapine when those compounds failed. App. 39a, 40a. The decision to make olanzapine did not involve a lot of thought or deliberation. In fact, as the evidence in the District Court showed, Lilly's scientists took a mere 30 minutes to identify olanzapine as a candidate for synthesis. C.A. A30326-28.

Olanzapine was one of the compounds covered by the genus of claim 1 of the '574 patent. As a result, Lilly recognized, even before it filed a patent application on olanzapine, that it faced an uphill battle in the PTO because claims to olanzapine would likely be rejected for *prima facie* obviousness over compounds in the prior art. C.A. A29075. For this reason, Lilly's patent department ordered a comparative dog toxicology study to find some property that could be used to distinguish olanzapine over the closest prior art compound, its adjacent homolog, Compound '222. C.A. A22855; *see* App. 90a.

Unfortunately for Lilly, the results of the toxicology study demonstrated that, as to most parameters of consequence, there was no statistically significant difference between olanzapine and Compound '222. Olanzapine and Compound '222 had very similar properties. App. 51a. And Lilly could not deny this fact. Indeed, a Lilly scientist left little doubt about this in a declaration submitted to the PTO in which he stated that it was his "considered view that there is little difference in properties of these two compounds when the data are viewed as a whole." C.A. A473; *see also* C.A. A475-481; C.A. A486. The only ostensible difference between the two compounds that Lilly could point to was a difference in cholesterol seen only in female dogs given the highest dose of Compound '222, a dose many times higher than the proposed human therapeutic dose. C.A. A72.

3. This matter was tried to the District Court from January 26, 2004 to February 12, 2004. At trial, DRL asserted that olanzapine would have been obvious to a person having ordinary skill in the art under 35 U.S.C. § 103(a). In particular, DRL argued that olanzapine was obvious in light of the '574 patent's disclosure of ethyl olanzapine (Compound '222), and the teaching in the Chakrabarti publications that a methyl, ethyl or iso-propyl group at the 2-position of the thiophene ring increased the antipsychotic activity of thienobenzodiazepine compounds. Based on these disclosures, DRL asserted that a person of ordinary skill in the art would have made olanzapine. The fact that ethyl olanzapine did not have optimal activity in screening assays for antipsychotic activity would not have dissuaded a person of ordinary skill from synthesizing olanzapine. The Chakrabarti publications listed three short-alkyl groups that enhanced antipsychotic activity, and a person of ordinary skill would have investigated compounds containing a 2-methyl

or 2-iso-propyl group when the 2-ethyl compound (Compound '222) showed low activity. In this normal course of research, olanzapine, which has a 2-methyl group, would have been, and in fact was, synthesized.

4. The District Court disagreed with DRL and found, in its April 14, 2005 decision, that the '382 patent was not obvious under 35 U.S.C. § 103(a). In rejecting DRL's argument, the District Court assessed the obviousness of the '382 patent using the framework of the teaching-suggestion-motivation ("TSM") test, and held that a finding of obviousness based on Compound '222 required a motivation in the prior art to select Compound '222 as a lead compound:

> To prevail on the theory that olanzapine was an obvious modification of compound '222, Defendants must establish by clear and convincing evidence that one of ordinary skill in the art would have been motivated to select compound '222 as a lead compound.

App. 220a-221a. The District Court found that a person of ordinary skill in the art would not have selected Compound '222 as a lead compound because the prior art taught away from unfluorinated compounds like Compound '222. App. 221a.

The District Court also found that it would not have been obvious to modify Compound '222 to arrive at olanzapine because the prior art would not have motivated a person of ordinary skill in the art to change the 2-ethyl substituent in Compound '222 to a 2-methyl group. App. 222a-223a. In doing so, the District Court discounted the teaching in the Chakrabarti publications about the desirability of a short-

alkyl group at the 2-position of a thienobenzodiazepine. Instead, focusing solely on the need for a motivation in the prior art to make the modification to Compound '222 that DRL asserted would have rendered olanzapine obvious, the District Court stated:

> Nothing in the prior art would have motivated one of ordinary skill in the art to change the ethyl group in compound '222 to a methyl group to arrive at olanzapine. While the '574 patent and *Chakrabarti 1980a* stated a preference for short alkyl groups in the context of fluorinated compounds, the ethyl group on compound '222 is already such a group. There was no teaching that any one short alkyl group was better than any other short alkyl group. There was, therefore, no motivation to change one of these groups to another of these groups.

App. 222a.

5. The Federal Circuit affirmed, and, like the District Court, it assessed the obviousness of olanzapine using the TSM test. The court applied the same lead compound requirement the District Court had asserted was necessary for a finding of obviousness. As a result, although the Federal Circuit conceded that "olanzapine is . . . the adjacent homolog of Compound '222," App. 15a, it nevertheless found that "the defendants have not shown that a person ordinarily skilled in this art would have selected Compound '222 as a lead compound." App. 16a. With respect to the teachings in the '574 patent and the Chakrabarti publications, which DRL asserted would have led a person of ordinary skill to modify Compound '222 to arrive at olanzapine, the court concluded

that "rather than providing the requisite motivation, the prior art taught away from selecting Compound '222 as a lead compound for further development." App. 16a.

The Federal Circuit's application of the TSM test, and in turn its requirement of an explicit preference for a lead compound in the prior art, foreclosed any objective consideration of the prior art. The court gave little consideration to the fact that, when olanzapine was developed, Lilly had made not only Compound '222 but also had substantial experience with flumezapine and ethyl flumezapine. Taken together, these compounds were the closest structurally to olanzapine. Viewed in this context, the teachings in the '574 patent and the Chakrabarti publications take on added weight. A person of ordinary skill in the art would have made olanzapine during the normal course of research into this series of compounds. However, by focusing only on why the prior art would have taught away from olanzapine, the Federal Circuit ignored common sense and reality in assessing the obviousness of olanzapine.

REASONS FOR GRANTING THE PETITION

I. A GVR ORDER IS APPROPRIATE IN LIGHT OF THIS COURT'S INTERVENING DECISION IN *KSR v. TELEFLEX*

The Court has recognized that GVR orders are appropriate in the following circumstances: (1) there have been "intervening developments, or recent developments that [the Court has] reason to believe the court below did not fully consider [that] reveal a reasonable probability that the decision below rests on a premise that the lower court would reject if given the opportunity for further consideration,"

(2) "it appears that such a redetermination may determine the ultimate outcome of the litigation," and (3) "the equities of the case" favor issuance of a GVR order. *Lawrence v. Chater*, 516 U.S. 163, 167-68 (1996) (per curiam).

Issuance of a GVR order in this case would be consistent with the Court's previous actions in patent cases where, as here, an intervening decision of this Court called into question a decision of the United States Court of Appeals for the Federal Circuit. This occurred, for example, following the Court's decision on prosecution history estoppel in *Festo v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002). *See, e.g., Intermatic Inc. v. Lamson & Sessions Co.*, 537 U.S. 1016 (2002); *Talbert Fuel Sys. Patents Co. v. Unocal Corp.*, 537 U.S. 802 (2002); *Creo Prods. Inc. v. Dainippon Screen Mfg. Co.*, 535 U.S. 1109 (2002).

KSR International Co. v. Teleflex Inc., 550 U.S. __, 127 S. Ct. 1727 (2007), issued approximately one month after the Federal Circuit denied the appellants' combined petition for panel rehearing and rehearing *en banc*. *KSR* establishes that the Federal Circuit's application of its TSM test to its assessment of obviousness in the decision below was impermissibly narrow and restrictive. This intervening development creates a reasonable probability that the decision below rests on a premise that the lower court would reject if given the opportunity for further consideration.

Moreover, reconsideration could be outcome-determinative. The rigid approach that blinded the Federal Circuit, as well as the District Court, to DRL's showing of obviousness also masked the weakness of the so-called "secondary considerations" of non-obviousness. Properly weighed under the Court's precedents, the secondary

considerations could not be deemed to have outweighed the strong evidence of obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966). Thus, a GVR order could determine the ultimate outcome of this litigation because reexamination under the *KSR* framework could result in the invalidation of the patent-in-suit.

II. *KSR* UNDERMINES THE DECISION BELOW

A. *KSR* Reaffirms the Primacy of the *Graham* Factors and This Court's Precedents Over the Federal Circuit's "Teaching-Suggestion-Motivation" Test.

In *KSR*, this Court expressly disapproved use of the Federal Circuit's TSM test as the primary test for assessing the obviousness of an invention, asserting instead that the *Graham* factors "continue to define the inquiry that controls."[2] *KSR*, 550 U.S. at __, 127 S. Ct. at 1734. "The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation. . . ." *Id.* at __, 127 S. Ct. at 1741. With respect to the TSM test's focus on "motivation," the Court stated that "[i]n determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls." *Id.* at ___, 127 S. Ct. at 1741-42.

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2. "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

Although not barring use of the TSM test outright, in *KSR* the Court determined that when applied as a "rigid and mandatory formula[]" the "TSM test is incompatible with our precedents." *Id.* at __, 127 S. Ct. at 1741. In this case, the Federal Circuit departed from this Court's precedents in favor of a constricted inquiry which is the antithesis of the "expansive and flexible approach" to the question of obviousness reaffirmed in *KSR*. *See id.* at __, 127 S. Ct. at 1739.

B. The Finding of Nonobviousness Below Was Predicated on a Particularly Rigid Version of the Teaching-Suggestion-Motivation Test.

1. The Federal Circuit's "Lead Compound" Requirement Is Contrary to the Principles Enunciated in *KSR*.

Although the Federal Circuit cited *Graham* as providing the "factual underpinnings" for the obviousness analysis, App. 12a-13a, *citing Graham*, 383 U.S. at 17, the court applied its own precedents instead. The court relied on a particularly restrictive version of the TSM test that it has adopted to assess the obviousness of pharmaceutical patents. Under this version of the TSM test, the Federal Circuit requires the patent challenger to establish as a threshold matter that the patentee would have been motivated to select one specific prior art compound as its "lead compound" for further development. *See* App. 15a-16a, *citing Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1344 (Fed. Cir. 2000). In the Federal Circuit's view, only a singular lead compound can provide the starting point for an obviousness analysis. *See* App. 16a. This approach is in direct conflict with the principles set forth in *KSR*.

The Federal Circuit largely endorsed the findings of the District Court, *see, e.g., id.* at 13a-15a, which framed the lead compound issue as follows: "To prevail on the theory that olanzapine was an obvious modification of compound '222, Defendants must establish by clear and convincing evidence that one of ordinary skill in the art would have been motivated to select compound 222 as a lead compound." *Id.* at 220a-221a. *KSR*, however, cautions against "limiting the analysis in this way." *KSR*, 550 U.S. at __, 127 S. Ct. at 1741.

The Federal Circuit did not analyze the prior art as required by *Graham* and reaffirmed in *KSR*. Rather, the court considered the prior art only from the viewpoint of how the art would have taught away from the choice of Compound '222 as a lead compound. *See* App. 16a ("[T]he defendants have not shown that a person ordinarily skilled in this art would have selected Compound '222 as a lead compound because it contained hydrogen rather than fluorine or chlorine. At the time of invention, the state of the art would have directed the person of ordinary skill in the art away from unfluorinated compounds like Compound '222."). This "teaching away" was premised on the litigation-inspired necessity for the lead compound to feature a so-called "neuroleptic substituent," defined as "an electron-withdrawing group" such as a halogen, for example, a fluorine or chlorine atom. *Id.* at 6a. By elevating teaching away above all else, the Federal Circuit erected an insurmountable obstacle to satisfying its lead compound requirement. The court's focus on teaching away was a "[r]igid preventative rule[]" that denied the court "recourse to common sense." *KSR*, 550 U.S. at __, 127 S. Ct. at 1742. The court essentially shut down the obviousness analysis before it could even begin.

The narrowness with which the Federal Circuit approached the obviousness inquiry can be seen in its insistence that only the supposed "preferences" taught in the prior art could be considered in identifying the requisite lead compound:

> Though the '574 patent disclosed Compound '222, the patent expressed *a preference* for halogen containing compounds and specifically those with a halogenated substituent on the benzene ring in a location analogous to the chlorine in clozapine. These teachings do not suggest or make obvious, among other things, olanzapine's hydrogen component. . . . Furthermore, the trial court found that a person of ordinary skill in the art would not have chosen Compound '222 as the beginning compound because it contained a hydrogen atom instead of a halogen atom, which again is not a preferred substituent.

App. 14a (emphasis in the original) (internal citations omitted). The Federal Circuit cited with approval the District Court's finding that "[w]hile Chakrabarti 1980a suggests that a chlorine atom in place of the fluorine atom would also enhance the compound's activity, *it does not specifically suggest that the same result could be obtained with a hydrogen atom.*" *Id.* at 13a-14a (emphasis added by the Federal Circuit). In contrast, according to *KSR*, when a court assesses the obviousness of a patent claiming a combination of elements from the prior art, "the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at ___, 127 S. Ct. at 1741.

The courts below went so far as to find that there could not be *any* lead compound within the entire class of "clozapine-like compounds," thereby halting the obviousness analysis in its tracks. *See* App. 15a ("The district court found that, at the relevant time, a person with ordinary skill in the art would not have expected any reasonable chance of success with other clozapine-like compounds."). The Federal Circuit added, "Beyond the nonobvious selection step, the prior art also did not suggest any of the other modifications necessary to reach olanzapine." *Id.* at 17a. Under the argument propounded by Lilly that was accepted below, a person of ordinary skill in the art would have given up before even starting. This flies in the face of both common sense and reality.

2. Adherence to the TSM Test Unduly Minimized Consideration of the Close Structural Relationship Between Olanzapine and Prior Art Compounds.

The rigid focus on teaching away and motivation blinded the courts below to the import of the close structural relationship between olanzapine and the prior art chemical compounds – especially Compound '222 and flumezapine. The Federal Circuit said that structural similarity did not control the obviousness analysis, App. 15a, 18a, and that it would "not ignore a relevant property of a compound in the obviousness calculus." *Id.* at 15a. However, the court went too far in the other direction, treating structural similarity instead almost as an afterthought. The court ignored the second *Graham* factor, *i.e.*, that it ascertain the differences between the prior art and the claims at issue, *see Graham*, 383 U.S. at 17, thus compounding its error in failing properly to consider the scope and content of the prior art.

Under the *KSR* framework, consistent with *Graham*, the starting point in the obviousness analysis should be the prior art landscape at the time that olanzapine was developed. This landscape included flumezapine, ethyl flumezapine and ethyl olanzapine (Compound '222), all of which had the same utility as olanzapine, that is, they exhibited antipsychotic properties, and was reflected in the '574 patent and the 1980 Chakrabarti publication. *See* App. 6a-8a. Moreover, the Chakrabarti 1980 publication taught that a short-alkyl substitution (defined as including a methyl or ethyl substituent) enhanced antipsychotic activity. C.A. A22701. This teaching, which was made more emphatic in subsequent Chakrabarti publications, received scant attention below.

Here the problem to be solved was synthesis of a chemical compound with potential for therapeutic use as an antipsychotic drug that did not exhibit disqualifying adverse side effects. Lilly's research scientists worked within the genus of compounds covered by Lilly's prior art '574 patent and built on the knowledge gained from their prior development efforts. It is undisputed that to look for new compounds, a medicinal chemist would vary substituents on known compounds with the expectation that the new compounds would have a similar constellation of properties, some of which might be more favorable and some less so. *See, e.g.*, C.A. A27165-66. Determining which of the resulting compounds are on the promising end of the spectrum is a matter of routine experimentation. "In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR*, 550 U.S. at ___, 127 S. Ct. at 1742. "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at __, 127 S. Ct. at 1740. As the Federal Circuit pointed out, "'[A] reasonable expectation of success,

not absolute predictability' supports a conclusion of obviousness." App. 13a (citation omitted).

Against this backdrop, a person of ordinary skill would have had "good reason to pursue the known options within his or her technical grasp," *KSR*, 550 U.S. at __, 127 S. Ct. at 1742, and synthesize olanzapine, a direct descendent of the prior art compounds ethyl flumezapine, flumezapine and ethyl olanzapine (Compound '222). Given this reality, making olanzapine was an "advance[] that would occur in the ordinary course without real innovation." *Id.* at __, 127 S. Ct. at 1741.

Even Lilly's medicinal chemistry expert, Dr. James Nichols, testified that olanzapine was the closest structural analog to prior art compounds Compound '222 and flumezapine, and that olanzapine varied from each of those compounds by only one substituent. C.A. A28545-46. This testimony also demonstrates that the Federal Circuit's reliance on *Yamanouchi* (as supporting the lead compound requirement) was as misplaced factually as it was legally. In likening this case to *Yamanouchi*, the Federal Circuit quoted a portion of the *Yamanouchi* decision faulting the patent challenger for not showing "sufficient motivation for one of ordinary skill in the art at the time of the invention to take any one of the following steps, let alone the entire complex combination. . . ." App. 15a-16a, *citing Yamanouchi*, 231 F.3d at 1344.

Unlike *Yamanouchi*, however, there were no multiple steps or any "complex combination" to reach olanzapine. Olanzapine differed in only one respect from each of flumezapine and ethyl olanzapine (Compound '222). *See* App. 7a-8a (describing each of those two prior art

compounds as varying by only one substitution from olanzapine). As Dr. Nichols grudgingly admitted, "If you just had to work with the substituents that were shown here [the chart of compounds reproduced on page 4, *supra*], you could put olanzapine together with those substituents that are shown there." C.A. A28545. Lilly's decision to make olanzapine followed this path.

3. The Federal Circuit's Application of the TSM Test Conflicts With the Reality of How Lilly's Research Chemists Actually Made Olanzapine.

The facts surrounding Lilly's decision to make olanzapine were undisputed but largely ignored by the courts below in favor of adherence to the TSM test. When olanzapine was first synthesized, Lilly's search for a safe and effective antipsychotic had been ongoing for several years. Lilly had previously advanced into development ethyl flumezapine and flumezapine, both of which were disclosed (as was Compound '222) in Lilly's prior art '574 patent as part of a large genus of compounds with antipsychotic properties. When flumezapine failed in clinical trials, the same research chemists at Lilly who had worked on ethyl flumezapine, flumezapine and ethyl olanzapine (Compound '222) "created another group of compounds in the same series in an effort to find another compound that could be developed as a clozapine replacement. . . ." App. 39a. The alternative compounds made and tested were unfluorinated as well as fluorinated. *Id.* at 40a. One of the compounds in that series was olanzapine. *Id.*

Two of the Lilly scientists named as inventors on the '382 patent, David Tupper and Terrence Hotten, testified that it took them only half an hour to come up with five

compounds they could make as a replacement for flumezapine. C.A. A30326-28. Dr. Tupper testified that "we considered what else we could do fairly quickly to make any other compounds. . . . We made what we could make with materials that we had on hand." C.A. A26108-09. Mr. Hotten testified similarly, "[I]t basically boils down to compounds which we could make relatively quickly from available starter materials we had at hand." C.A. A30175. One of those replacement compounds was olanzapine, which was "selected by a method of elimination from that group of five." C.A. A30203.

The synthesis of olanzapine itself was relatively straightforward and was quickly accomplished: "We had done quite a lot of work over the years on this series. So therefore we had a fairly straightforward synthesis of the compound by then." C.A. A30330. Mr. Hotten noted the scientists' preference for a methyl rather than an ethyl substituent, recalling that since one compound with an ethyl had run into toxicity problems, "our sort of general feeling was that it would be better to use methyls, as flumezapine had passed animal toxicity without any problems." C.A. A30208; *see id.* at A30209-10.

4. The Real Hindsight Bias Was the Purported Need for a Neuroleptic Substituent.

In *KSR* the Court cautioned against "the risk of courts and patent examiners falling prey to hindsight bias." *KSR*, 550 U.S. at __, 127 S. Ct. at 1742. That warning was not heeded here. The hindsight in this case was the acceptance by the courts below of the litigation-inspired theory that, because the purported need for a neuroleptic substituent precluded the selection of Compound '222 as a lead

compound, the synthesis of olanzapine could not have been obvious. Common sense suggests that, when Lilly was trying to convince the PTO to grant it a patent for olanzapine in the first place, it would have used the most favorable arguments in its arsenal. But Lilly did not predicate any argument for patentability on the purported teaching away from olanzapine in the prior art.

Instead, the prosecution history of the '382 patent demonstrates that both Lilly and the PTO recognized that the close structural relationship between olanzapine and Compound '222 augured against the patentability of olanzapine. The patent examiner rejected olanzapine as obvious over the '574 patent in view of the Chakrabarti 1980 publication because:

> [i]t would have been obvious to one with ordinary skill in the art to replace the 2-ethyl substituent on the homologous species [compound '222] taught in [the '574 patent] with the 2-methyl substituent in order to obtain the instant compound [olanzapine] because [Chakrabarti 1980a] specifically suggests to one with ordinary skill in the art that this type of substituent is preferably [sic] to increase [central nervous system] activity.

App. 46a. The courts below ignored the examiner's finding, and reached the *opposite* conclusion, namely that "the prior art supplied no motivation to change the 2-ethyl in Compound '222 to a 2-methyl." App. 14a-15a, citing 364 F. Supp. 2d at 849-50 (App. 79a-80a).

The unrebutted evidence at trial showed that from the time that olanzapine was first synthesized, it was well and widely understood within Lilly that olanzapine was covered by Lilly's '574 patent. *See, e.g.*, C.A. A26141-42; C.A. A30287-88; C.A. A2269; C.A. A2274. Lilly had always planned to argue to the PTO that olanzapine was patentable based on a showing of unexpected results. In fact, Lilly began preparing its response to the examiner's *prima facie* obviousness rejection before even receiving it, and did not seriously contest the *prima facie* obviousness issue in the PTO.

Lilly never argued to the PTO that it was surprising and unexpected that olanzapine exhibited antipsychotic properties even though it was not a fluorinated compound. Rather, Lilly relied on a comparative dog toxicology study commissioned by the patent department in the hope that the study would uncover some property that Lilly could use to tout olanzapine as unexpectedly superior as compared to the closest prior art – that is, Compound '222 – although it was hard-pressed to find any difference in most parameters of consequence. *See* App. 44a, 47a-55a.

Yet, instead of looking to the contemporaneous events recorded in the prosecution history and in Lilly's internal documents, the Federal Circuit adhered to its TSM test. *See, e.g., id.* at 16a ("[R]ather than providing the requisite motivation, the prior art taught away from selecting Compound '222 as a lead compound for further development."). The Court of Appeals thus "engage[d] in the very hindsight bias" that *KSR* says "must be avoided." *KSR*, 550 U.S. at ___, 127 S. Ct. at 1745.

III. PROPERLY WEIGHED, THE SECONDARY CONSIDERATIONS WOULD NOT OVERCOME THE CLEAR EVIDENCE OF OBVIOUSNESS

Consideration of secondary considerations such as commercial success, long-felt but unmet needs and the failure of others is one hedge against inappropriate reliance on hindsight because such factors can "give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham*, 383 U.S. at 17-18. Having improperly disregarded the evidence of obviousness, the courts below could not properly weigh the evidence of secondary considerations. The secondary considerations were, in fact, quite minimal.

Lilly's expert, Dr. Schulz, admitted at trial that risperidone was the first drug to meet the need for a safe, atypical antipsychotic drug. C.A. A28661-62. Risperidone, developed by Janssen Pharmaceuticals, was first prescribed to patients some two and a half years before olanzapine. App. 86a. Risperidone received industry acclaim, as did olanzapine. *See id.* at 88a. Thus, Janssen, the manufacturer of risperidone, did not fail in its efforts to develop a safe atypical antipsychotic drug.

Although the Court of Appeals cited olanzapine as having "a reasonable amount of commercial success," App. 19a, the District Court found that the evidence of commercial success did not weigh in favor of either side. App. 88a. In any event, "commercial success without invention will not make patentability." *Great Atlantic & Pacific Tea Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 153 (1950); *see also Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 61 (1969). Moreover, Lilly was able to

block its competitors from working in the area of thienobenzodiazepines during the term of its '574 patent, *see* C.A. A26470, further diminishing any inference of non-obviousness that could be drawn from any commercial success of olanzapine. *See Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir.), *cert. denied*, 126 S. Ct. 488 (2005).

The evidence of unexpected results was thin. It was apparent from the prosecution history of the '382 patent that olanzapine and Compound '222 were similar in most parameters tested. *See, e.g.*, App. 49a-51a. It was only in a dog toxicology study, and even then only in a group of four female dogs in the highest dosage group – a dosage far above the projected therapeutic dose – that an increase in cholesterol levels was found in dogs given Compound '222 rather than olanzapine. *See id.* Three other groups of dogs given Compound '222 showed no increase in cholesterol compared to the corresponding groups given olanzapine in that same study. *See, e.g., id.* at 52a-53a. The lack of real-world significance to that "unexpected" result can be seen, for example, in a subsequent Lilly-funded study on humans that "found statistically significant increases in mean cholesterol levels after treatment with olanzapine. . . ." C.A. A25093.

In short, if the Federal Circuit were to re-evaluate the secondary considerations, it should conclude that such indicia could not outweigh the strong evidence of the obviousness of olanzapine. Thus, issuance of a GVR order could be outcome-determinative.

IV. THE EQUITIES FAVOR ISSUANCE OF A GVR ORDER

The real innovation in thienobenzodiazepine compounds was represented in Lilly's '574 patent and in the Chakrabarti 1980 publication. Making olanzapine, particularly where it was so close to compounds that were already known in the art, was the type of advance that would occur as a matter of course, as was borne out by the actual facts. Lilly's right to preclude others from making olanzapine should have ended with the expiration of the '574 patent.

A goal of the 1984 Hatch-Waxman amendments to the Food, Drug and Cosmetic Act, 21 U.S.C. § 355, is "to enable new drugs to be marketed more cheaply and quickly." *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990). A remand for reconsideration by the Court of Appeals could result in the invalidation of Lilly's undeserved patent for olanzapine and provide price relief to the public still paying artificially high prices for this drug.

CONCLUSION

For the reasons stated above, the petition should be granted, and the judgment of the Court of Appeals vacated in light of *KSR International Co. v. Teleflex Inc.*, 550 U.S. __, 127 S. Ct. 1727 (2007).

Respectfully submitted,

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